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## Remarks

Claim 1-6 are currently pending in the application. The amendments to the pending claims were made to clarify the scope of coverage and more particularly point out and distinctly claim the present invention. These amendments are made without prejudice, do not constitute amendments to overcome any prior art rejections, and do not present any new matter.

## Discussion of the 35 U.S.C. § 112, Second Paragraph Rejection

Claims 3 and 6 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this ground of rejection. With respect to claim 3, the Office Action asserts that it is vague and indefinite in the reliance on the terms p21, p27, and p16 as the only means of characterizing the biological markers upon which the method depends. The Office Action further states that the designation of "pX" is conventional in the art for a protein having a molecular weight of X. Therefore, the Office Action alleges that the metes and bounds cannot be determined. However, contrary to this assertion, claim 3 is dependant on claim 1, and therefore incorporates all of the limitation of claim 1. Thus, p21, p27, and p16 are not proteins cited out of context, but rather are defined by claim 1 as biological markers associated with senescence, apoptosis, or terminal differentiation. Thus the names p21, p27, and p16 are not only characterized by their molecular weight, but also by the fact that they are biological markers. In fact, the acceptance of the names p21, p27, and p16 by those skilled in the art, as they relate to biological markers associated with senescence, apoptosis, or terminal differentiation, is evident from the numerous references cited by the Examiner in support of the

35 U.S.C. § 103 rejections. Accordingly, Applicant respectfully requests withdrawal of this rejection and requests reconsideration of the claims.

With respect to the rejection of claim 6, the Office Action stated that the claim is in improper form for failing to provide sufficient antecedent basis for the limitation "biological sample". Although not acquiescing to this ground of rejection or the Examiner's reasoning supporting the rejection, Applicants have amended claims 6 to better clarify the invention. Applicants respectfully contend that this amendment has overcome the asserted ground of rejection.

**Discussion of the 35 U.S.C. § 103(a) Rejection(s)**

Claims 1, 2, 5, and 6 are rejected under 35 U.S.C. § 103(a) as being obvious over Bacus (U.S. 5,288,477) ("Bacus I") in view of the abstract of Bacus *et al.* (Breast Cancer Research and Treatment, 1999, vol.57, page 55) ("Bacus II"); Warri *et al.* (J. Nat'l Cancer Inst., 1993, vol. 85, pp. 1412-1418) ("Warri"); the abstract of Wu (Cancer Res., 1996, vol. 16, pp. 2233-2239) ("Wu"); the abstract of Fornier *et al.* (Oncology, 1999, vol. 13, pp 647-658) ("Fornier") and the abstract of Lebwohl *et al.* (Annals of Oncology, 1999, 10 suppl. 6, pp 139-146) ("Lebwohl"). Applicants respectfully traverse this rejection.

An analysis for obviousness requires a determination of the scope and content of the prior art, the differences between the prior art and the claims at issue must be ascertained, and the level of ordinary skill in the pertinent art must be resolved. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). To establish a *prima facie* case of obviousness, the Office must show three basic criteria: (1) there must be a suggestion or motivation to combine the reference teachings; (2) there must

be a reasonable expectation of succ ss; and (3) all of the claimed limitations must be taught or suggested in the combined prior art references. M.P.E.P. § 2143.

The present invention is directed to a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual, wherein said method comprises collecting a tissue or cell sample from an individual both before and after exposing the individual to a chemotherapeutic or chemopreventive agent, immunohistochemically staining both samples using a detectably labeled antibody directed against a biological marker associated with senescence, apoptosis, or terminal differentiation, measuring the optical density of the stained samples, and determining whether expression of the biological marker was increased following exposure to the chemotherapeutic or chemopreventive agent.

None of the cited references, alone or in combination, teach or suggest the instantly claimed method. Bacus 1 teaches a method for *prognosticating* the effectiveness of a therapeutic agent in the treatment of a cancer by measuring the ability of the therapeutic agent to induce terminal differentiation wherein malignant cells of the cancer overexpress an oncogene product, the method comprising obtaining from a human having cancer *a single* biopsy comprising viable malignant cells which overexpress at least one oncogene product; dividing said biopsy into a first and second portion; treating the first portion with a compound having specific binding affinity for said oncogene product; maintaining said first and second portions in physiologically acceptable medium for an amount of time sufficient to induce maturation in the viable malignant cells of the first portion; and comparing the percentage of cells in the first portion which exhibit markers of terminal differentiation with the percentage of cells in the second portion which exhibit markers of terminal differentiation, wherein the effectiveness of treatment is correlated

with the degree of terminal cell differentiation. Accordingly, because Bacus I only teaches obtaining a *single* biopsy from a human having a cancer, it certainly does not teach or suggest the presently claimed methods that require collecting *both* a first and second tissue or cell sample from an individual, *both* before and after exposing the individual to a chemotherapeutic or chemopreventive agent. Further, Bacus I teaches how to *prognosticate* or *predict* a response to a chemotherapy, whereas the present invention is drawn to methods of determining the *actual* response to a chemotherapy. Thus, Bacus I does not teach or suggest the presently claimed invention.

The deficiencies of Bacus I are not overcome by the combination with the other cited art. Warri describes the use of Toremifene, an antiestrogen, to cause growth inhibition of estrogen-sensitive breast cancer cells by inducing some cells to undergo apoptosis and by inhibiting other cells from entering mitosis. The Office Action cites Warri for the proposition that methods for treating breast cancer *should* target the induction of apoptosis to breast cancer cells, even though the actually conclusion of Warri is only that apoptosis "provides a *potential* new therapeutic approach for treating breast cancer." Nevertheless, Warri does not teach a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual that targets the induction of apoptosis, much less any chemotherapeutic or chemopreventive agent. Further, Warri does not teach or even suggest the presently claimed invention of collecting both a first and second tissue or cell sample from an individual, both before and after exposing the individual to a chemotherapeutic or chemopreventive agent, and measuring the optical density of cells after immunohistochemically staining them with a detectably labeled antibody directed against a biological marker associated with, *inter alia*, apoptosis.

Wu discloses that apoptosis *and* angiogenesis *may* be valuable markers for response in patients having primary or adjuvant chemotherapy for breast cancer because tumor growth is dependent on angiogenesis and cell death in tumors is commonly attributed to the induction of apoptosis. Wu specifically teaches "the *prognostic* significance of apoptosis and angiogenesis in breast cancer," and that indicators of apoptosis "may have *predictive* value for the response to anticancer treatments." However, Wu does not teach, much less suggest, that an actual response to administration of a chemotherapeutic or chemopreventive agent could be *determined* by collecting a first and second tissue or cell sample from an individual before and after exposure to the agent. Further, Wu certainly does not teach methods of the claimed invention whereby a response to a chemotherapeutic or chemopreventive agent is determined by immunohistochemically measuring the optical density of a cell stained with a detectably labeled antibody directed against a biological marker associated with senescence, apoptosis, or termination differentiation. In fact, Wu does not even teach *any* biological marker associated with senescence, apoptosis, or termination differentiation that could even be detected to predict the response to an anticancer agent, but rather makes a broad statement that apoptosis itself could be a valuable marker for response.

Fornier is cited by the Office Action as teaching that clinical studies were underway in the treatment by the *combined* administration of Herceptin and Taxol. Fornier, however, also cautions that "it may be time to reconsider the belief that combination chemotherapy is the gold standard of treatment," and that current combination treatments "should be used only in the context of clinical trials." Notably, the present invention is not directed to methods or pharmaceutical compositions for treatment, and Fornier does not teach methods for identifying treatment efficacy by assaying for markers of senescence, apoptosis or terminal differentiation.

Fornier is further cited for the fact that it identifies Herceptin as a humanized antibody directed to the Her-2/neu protein. However, Herceptin is disclosed as being a *chemotherapeutic or chemopreventive agent*, not as a *detectably labeled antibody* that could be used in immunohistochemistry. Therefore, a skilled artisan would not be motivated based on Fornier to use Herceptin, or any other humanized antibody, to practice the claimed invention.

Lebwohl is cited for the fact that the combined administration of Herceptin and doxorubicin results in higher response rate and prolonged the disease progression when compared to a single chemotherapy alone. Lebwohl takes a more positive stance regarding the state of combination therapy, stating that combination therapy "provides a new standard for the first line treatment of metastatic breast cancer." Both Fornier and Lebwohl teach the combined administration of Herceptin with other chemotherapies. However, like Fornier Lebwohl does not teach a method for determining a response of administration to an individual receiving such combination therapies, much less any other chemotherapeutic or chemopreventive agent, either administered alone or in combination. Certainly, therefore, neither Fornier nor Lebwohl teach or even suggest the presently claimed invention of collecting both a first and second tissue or cell sample from an individual, both before and after exposing the individual to a chemotherapeutic or chemopreventive agent, and measuring the optical density of cells after immunohistochemically staining them with a detectably labeled antibody directed against a biological marker associated with, *inter alia*, apoptosis.

Bacus II is cited for the proposition that Taxol and doxorubicin affect apoptotic signaling in breast cancer cells by different mechanisms, that Herceptin inhibits PI-3 kinase, and that over-expression of HER-2/neu and HER-3 will affect a patient's response to these chemotherapeutic agents. Bacus II, however, does not teach a method of determining a response of administration

to an individual receiving Taxol, doxorubicin, and/or Herceptin, much less any other chemotherapeutic or chemopreventive agent.

Thus, Applicants respectfully contend that the Office Action has failed to establish a *primia facie* case of obviousness because first, there is no teaching, suggestion or motivation to combine the cited reference, and second, even if the references are not improperly combined, all of claim limitations are not taught or suggested by Bacus I, Warri, Wu, Fornier, Lebwohl, and Bacus II. The Office Action argues that it would have been obvious to evaluate a patient's response to chemotherapy by means of: a) obtaining a sample of cells or tissues from the patient before chemotherapy and obtaining a second sample of cells or tissues from said patient after chemotherapy; b) quantitating the presence of Her-2/neu on the surface of said cells by means of an antibody labeled with a fluorophore or a chromogen; c) quantitating the total number of cells by staining DNA; and d) subjecting the cells to image analysis so that a percentage of cells expressing both labeled antibody and labeled DNA can be quantified in order to measure the effectiveness of combined therapy in the induction of apoptosis in breast cancer cells in patients having undergone therapy. Further, the Office Action argues that a skilled artisan would have been motivated to do so with a reasonable expectation of success by teachings of Lebwohl and Fornier regarding recent clinical trials using the combination of Herceptin with Taxol and doxorubicin, or by the teaching of Bacus II regarding the interaction with Herceptin on the apoptotic pathway, or the teaching of Warri for the targeting of apoptosis, or the teaching of Wu for the correlation between apoptosis and response to chemotherapy for breast cancer, and the teaching of Bacus I for the targeting of stabilization and a reduction of a cell population in a method of treating breast cancer. However, the mere description in Bacus I of using image analysis to *predict* whether a chemotherapeutic agent would be effective for a patient does not

amount to a teaching or suggestion to determine or monitor a *response* of an individual to the administration of a chemotherapeutic agent. The secondary references do not cure this infirmity. Warri, Wu, Fornier, Lebwohl, and Bacus II are merely concerned with describing specific treatments of breast cancer by targeting apoptosis. None of these references contemplate or teach methods for *determining* or monitoring a response to the specific treatments disclosed in the references. *A fortiori*, the references certainly do not teach or even contemplate the instantly-claimed methods of determining a response by immunohistochemically staining two samples removed from an individual, both before and after exposure to the treatment, and measuring the optical density of the stained cells. In the absence of such teaching, Applicants contend there was simply no motivation to combine these references as the Office Action suggests.

Moreover, the mere fact that individual references *can* be combined does not render the resultant combination obvious *unless* the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680; 16 USPQ2d 1430 (Fed. Cir. 1990). Therefore, although the prior art may be capable of being combined or modified, there *must* be a suggestion or motivation in the reference to do so. *In re Mills*, 916 F.2d at 682; see also *In re Fritch*, 972 F.2d 1260 (Fed. Cir. 1992); M.P.E.P. § 2143.01. Moreover, even if the references relied upon teach that aspects of the claimed invention were individually known in the art, this alone is not sufficient to establish a *prima facie* case of obviousness, without some objective reason (outside the teachings of Applicants' specification) to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1999); M.P.E.P. § 2143.01.

In fact, the Federal Circuit "has recently reemphasized the importance of the motivation to combine . . . ." *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343, 56 USPQ2d 1641, 1644 (Fed. Cir. 2000). In making a 35 U.S.C. § 103(a) determination,

"[o]bviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teachings, suggestion, or incentive supporting the combination." *In re Greiger*, 815 F.2d 686, 688, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). Also, "'broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence'[of obviousness]" *Ecolochem, Inc. v. S. Calif. Edison Co.*, 227 F.3d 1361, 1372, 56 U.S.P.Q.2d 1065, 1073 (Fed. Cir. 2000) (quoting *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999)).

A recent decision by the Federal Circuit further dictates that the teaching, motivation, or suggestion to combine *cannot* be based solely on the "common knowledge and common sense" of a skilled artisan, but rather must be based on the evidence found in the record. *In re Lee*, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002). Thus, if the reason to combine is common and well known, the Office should be able to cite a reference establishing that fact. Accordingly, "to establish obviousness based on a combination of the elements disclosed in the prior art, there *must* be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant," to one of ordinary skill in the art. *In re Kotzab*, 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000) (*emphasis added*). In addition, "'the showing of combinability must be clear and particular.'" *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 665, 57 U.S.P.Q.2d 1161, 1168 (Fed. Cir. 2000) (quoting *Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2d at 1017).

Applicant respectfully submits that the Office Action has engaged in impermissible hindsight to support its argument. In this regard, the Federal Circuit dictates, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious. This

court has previously stated that '[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fritch*, 23 U.S.P.Q.2d 1780, 1784 (Fed Cir. 1992) (citations omitted) (quoting *In re Fine*, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988)); *see also Para-Ordnance Mfg., Inc. v. SGS Imposters Int'l Inc.*, 37 U.S.P.Q. 1237, 1239 (Fed. Cir. 1995) ("Obviousness may not be established using hindsight or in view of the teachings or suggestions of the inventor."); *Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods. Inc.*, 30 U.S.P.Q.2d 1377 (Fed. Cir. 1993) ("The motivation to combine references cannot come from the invention itself."); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time."). Applicants respectfully submit that what the law precludes is precisely the basis for the asserted obviousness rejection.

For the reasons set forth above, none of the references cited in support of this ground of rejection, Bacus I, Warri, Wu, Fornier, Lebwohl, and Bacus II, taken either alone or in any combination, disclose, either individually or in combination, a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests withdrawal of this rejection and requests reconsideration of the claims.

Claims 1-3 , 5, and 6 are rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Bacus I in view of Bacus II; Warri; Wu; Fornier and Lebwohl, and further in view of Caffo et al (Clinical Cancer Res., 1996, vol. 2, pp. 1591-1599) ("Caffo"), the abstract of el-Deiry et al. (Cancer Res. 1995, Vol. 55, pp. 2910-2919) ("el-Deiry"), the abstract of Thor et al.

(J. Nat'l Can. Inst., 1992, Vol. 84, pp. 845-855) ("Thor"), and the abstract of Shetty et al. (Leukemia Res., 1996, vol. 20, pp. 11-12) ("Shetty"). Applicants respectfully traverse this rejection.

None of the additionally-cited references, taken alone or in any combination with the earlier-discussed references, teach or suggest the instantly claimed method. The teachings and deficiencies, as related to the present invention, of Bacus I, Bacus II, Warri, Wu, Fornier, and Lebwohl are thoroughly discussed above. In this ground of rejection, the Warri reference is cited in addition for the proposition that TGF-beta is a biological marker for apoptosis because apoptotic changes were connected with an elevation in TGF-beta mRNA. The Office Action assets that it "is reasonable to conclude that TGF-beta protein was elevated as a result of the elevation of TGF-beta mRNA." However, no support for this assertion is provided. Indeed, Warri itself acknowledged that "[t]oremifene had a slight effect on TGF-ß1 expression in MCF-1 tumors," and that "[t]he amount of TGF-ß1 mRNA per cell in these tumors was unchanged 10 days after toremifene administration." Without providing support for the assertion that the level of TGF-ß1 protein are increased as a result of treatment with toremifene, especially in view of the express teaching that toremifene only had a slight affect on TGF-ß1, one skilled in the art would not have understood Warri as providing the suggestion or motivation to treat TGF-ß1 as a biological marker for apoptosis. If additional facts or evidence in this regard are known to the Examiner, or any other Patent Office employee, Applicants respectfully request such facts or evidence be made of record, pursuant to the provisions of 37 C.F.R. §1.104(d)(2).

The deficiencies of Bacus I, Bacus II, Warri, Wu, Fornier, and Lebwohl are not overcome by the combination with the other cited art. Caffo discloses that chemotherapy or radiotherapy induces DNA damage that activates p53 function. In addition, Caffo teaches a method of

confirming the functional status of p53 by measuring downstream effector functions such as the activation of p21. Caffo concludes that the p21/p53 phenotype may be of clinical relevance concerning the response to chemotherapy/hormone therapy. However, Caffo also explains that the study was conducted to investigate the possibility that "p21 could be an interesting *prognostic* or *predictive* marker." *Caffo* at 1598 (emphasis added). In fact, Caffo concludes that the "combined evaluation of p53 and p21 expression may provide *prognostic* information which is more accurate than the evaluation of p53 expression alone." *Caffo* at 1596 (emphasis added). Accordingly, because Caffo only teaches that p21 can be used as a *predictive* marker, it certainly does not teach or suggest a method of determining a *response* to administration of a chemotherapeutic or chemopreventive agent to an individual, much less a method of the present invention.

el-Deiry is cited as teaching that antibodies to human p21 can be used in immunohistochemical analysis to monitor the effects of radiation-induced damage. Thor is cited as teaching that antibodies to human p53 can be used in immunohistochemical analysis to detect p53 in archival samples of breast carcinomas. Shetty is cited as teaching that antibodies to human TGF-beta can be used in immunohistochemical analysis to monitor the expression of TGF-beta in cells of myelodysplastic syndromes. However, neither el-Deiry, Thor, nor Shetty teach that the disclosed antibodies could be used for determining a *response* to administration of a chemotherapeutic or chemopreventive agent, much less teach or suggest that such an antibody could be used in a method of the claimed invention (which methods are also nowhere disclosed in this or any other of the cited references).

Thus, Applicants respectfully submit that the Office Action has failed to establish a *primia facie* case of obviousness against the rejected claims, *inter alia* because all of claim

limitations are not taught or suggested by Bacus I, in view of Bacus II, Warri, Wu, Fornier, Lebwohl, and further in view of Caffo, el-Deiry, Thor, and Shetty. The Office Action argues that it would have been obvious to one of ordinary skill to include antibodies that bind to p21, p53, and TGF-beta to the method rendered obvious by the combination of Bacus I, Bacus II, Warri, Fornier, and Lebwohl. Further, the Office Action argues that a skilled artisan would have been motivated to do so with a reasonable expectation of success by the teachings of Warri regarding the up-regulation of expression of TGF-beta after treatment with an anti-estrogen compound, the teachings of Caffo on the importance of the p21 and p53 phenotypes of breast cancer in response to chemotherapy, and the teachings of el-Deiry, Thor, and Shetty for teaching that antibodies to p21, p53, and TGF-beta are available for immunohistochemistry. The Office Action also states, without explanation, that one skilled in the art would conclude that if the remaining tumor cells were p21 negative/p53 positive, chemotherapy should be stopped. However, for reasons set forth in detail above, Bacus I, Bacus II, Warri, Wu, Fornier, and Lebwohl do not teach or suggest a method for determining or monitoring a response of an individual to the administration of a chemotherapeutic or chemopreventive agent. In view of the fact that Caffo is solely concerned with identifying whether p21 *could* be a *predictive* marker for chemotherapy, the reference adds nothing to the fatally-defective teachings of the Bacus I, Bacus II, Warri, Wu, Fornier, and Lebwohl references, and by itself it does not teach or suggest methods of determining or monitoring the *response* to a chemotherapy. Furthermore, because el-Deiry, Thor, and Shetty merely describe specific antibodies to biological markers associated with senescence, apoptosis, and/or terminal differentiation, they do not contemplate a method for determining or monitoring a response using these specific antibodies, much less a method of the present invention of determining a response by immunohistochemically staining two samples removed from an

individual, both before and after exposure to the treatment, and measuring the optical density of the stained cells. In the absence of such teaching, there was simply no motivation to combine these references, as the Office Action suggests. Once again, it is Applicant's position that the obviousness rejection based on this combination of references in the Office Action has been achieved through the use of impermissible hindsight, and that the pending claims are non-obvious over the cited prior art, taken alone or in any combination.

For the reasons set forth above, Bacus I, Bacus II, Warri, Wu, Fornier, Lebwohl, Caffo, el-Deiry, Thor, and Shetty do not disclose, either individually or in combination, a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests withdrawal of this rejection and requests reconsideration of the claims.

Claims 1-3 , 5, and 6 are rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Bacus I in view of Bacus II, Warri, Wu, Fornier, and Lebwohl, and further in view of Hochhauser (Anti-Cancer Drugs, 1997, Vol. 8., pp. 903-910) ("Hochhauser"), the abstract of Ohtani *et al.* (Cancer, 1999, vol. 85, pp. 1711-1718) ("Ohtani"), and the abstract of Emig *et al.* (British J. of Cancer, 1998, Vol. 78, pp. 1661-1668) ("Emig"). Applicants respectfully traverse this rejection.

None of the additionally-cited references, taken alone or in any combination with the earlier-discussed references, teach or suggest the instantly claimed method. The teachings and deficiencies, as related to the present invention, of Bacus I, Bacus II, Warri, Wu, Fornier, and Lebwohl are discussed in detail above. The deficiencies of Bacus I, Bacus II, Warri, Wu, Fornier, and Lebwohl are not overcome by the combination with the other cited art.

Hochhauser discloses that alterations in cell cycle genes can sensitize cells to apoptosis following treatment with chemotherapeutic agents. Hochhauser also discloses that induction of p16 expression results in reversible cell cycle arrest, and that expression of p27 in tumors is related to acquired drug resistance to chemotherapeutic agents. Thus, the Hochhauser reference merely reports gene expression changes that accompany apoptosis. However, Hochhauser does not teach or suggest any *methods* that utilize the information regarding p16 or p27, much less a method of the present invention for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual (which methods are also nowhere disclosed in this or any other of the cited references).

Ohtani is cited as teaching that antibodies to human p27 can be used in immunohistochemical analysis to monitor the expression of p27 in gastric cancer cells. However, Ohtani teaches that *decreased* expression of p27Kip1 was an important factor in *predicting* a poor prognosis for patients with non-early stage gastric carcinoma. Further, Ohtani does not teach or suggest the effects of any chemotherapeutic or chemopreventive agents, much less the use of p27 as a marker to determine a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Ohtani is completely silent in all respects relating to Applicants' claimed methods.

The Emig reference is cited as teaching that antibodies to human p16 can be used in immunohistochemical analysis to monitor the expression of p16 in breast cancer cells. Similar to Ohtani, Emig does not teach or suggest the effects of any chemotherapeutic or chemopreventive agents. Moreover, neither Emig nor Ohtani teach that the disclosed antibodies could be used for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual, much less teach the claimed invention of collecting a tissue or cell sample from an

individual before and after exposure to an agent and measuring the optical density of the cells via immunohistochemistry after staining with an antibody that has been detectably labeled.

Thus, Applicants respectfully submit that the Office Action has failed to establish a *primia facie* case of obviousness against the rejected claims, *inter alia* because all of claim limitations are not taught or suggested by the cited references. The Office Action argues that it would have been obvious to one of ordinary skill to include the antibodies to p16 and p27 in the method rendered obvious by the combination of Bacus I, Bacus II, Warri, Fornier, and Lebwohl. Further, the Office Action argues that a skilled artisan would have been motivated to do so with a reasonable expectation of success by the teachings of Hochhauser of the inverse relationship between the expression of p27 and p16 and the induction of apoptosis by chemotherapeutic agents, and the teachings of Ohtani and Emig for teaching that antibodies to p16 and p27 are available for immunohistochemistry. However, as set forth in detail above, none of the primary references (Bacus I, Bacus II, Warri, Wu, Fornier, and Lebwohl) teach or suggest a method for determining or monitoring a response of an individual to the administration of a chemotherapeutic or chemopreventive agent. Addition of the Hochhauser reference does nothing to correct the insufficiencies of the primary references, since Hochhauser merely describes the altered expression of cell cycle regulatory genes related to cancer. Hochhauser does not teach or suggest any methods at all, much less methods of determining or monitoring the response to a chemotherapy. Furthermore, because Ohtani and Emig merely describe specific antibodies to biological markers associated with senescence, apoptosis, and/or terminal differentiation, they also do not contemplate methods for determining or monitoring a response to chemotherapy or chemoprevention using these specific antibodies, much less the claimed methods of determining a response by immunohistochemically staining two samples removed from an individual, both

before and after exposure to the treatment, and measuring the optical density of the stained cells. In the absence of such teaching, Applicants contend there was simply no motivation to combine these references. Once again, it is Applicant's position that the obviousness rejection based on this combination of references in the Office Action has been achieved through the use of impermissible hindsight, and that the pending claims are non-obvious over the cited prior art, taken alone or in any combination.

For the reasons set forth above, Bacus I, Bacus II, Warri, Wu, Fornier, Lebwohl, Hochhauser, Ohtani, and Emig do not disclose, either individually or in combination, a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests withdrawal of this rejection and requests reconsideration of the claims.

Claims 1, 2, 4, and 5 are rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Meyn et al. (AntiCancer Drugs, 1995, vol. 6, pp. 443-450) ("Meyn") in view of Riss (U.S. 6,350,452) ("Riss") and Bjorklund et al. (WO 99/16789) ("Bjorklund") and Schlossman et al. (U.S. 5,935,801) ("Schlossman") and Desjardins (U.S. 5,972,622) ("Desjardins"). Applicants respectfully traverse this rejection.

None of the cited references, either alone or in combination, teach the claimed invention. Applicants note that the newly-cited references are not discussed with regard to the teachings of the other cited references, that the Action is thereby asserting a separate and independent ground of rejecting the pending claims for obviousness based on these references, and that the newly-cited references are not being combined with the other cited references discussed above.

Meyn discloses that seven different murine tumors were examined after treatment, and that a mammary carcinoma and a ovarian adenocarcinoma underwent apoptosis in response to treatment. The Office Action asserts that Meyn concludes that that apoptosis is a feature of tumor response to chemotherapy in vivo. However, Meyn's conclusion is actually more tentative, stating "that apoptosis *may* be a feature of tumor response to chemotherapy in vivo . . . ." Nevertheless, Meyn merely teaches that apoptosis is a *potential* response to treatment with a chemotherapeutic or chemopreventive agent, and does not teach, much less suggest, using this observed result in any method related to either predicting or monitoring the response to such a chemotherapeutic or chemopreventive agent. Meyn, therefore, certainly does not teach or suggest a method of the present invention.

The deficiencies of Meyn are not overcome by the combination with the other cited art. Riss is cited for teaching antibodies that recognize an epitope of the PARP protein formed by cleavage of said protein by caspases. Riss also discloses the detection of apoptosis in a cell or group of cells with the use of this antibody. However, Rissi only teaches specific uses of this antibody, including the use of the antibody to screen for possible anti-apoptotic agents. Rissi does not teach or suggest any methods related to determining the response to treatment with a chemotherapeutic or chemopreventive agent, much less a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual.

Björklund discloses a method for detecting early apoptotic changes in epithelial cells by contacting the cells with the M30 antibody that binds to an epitope of keratin 18 exposed after cleavage by caspases. Björklund also teaches methods including a determination of the rate of apoptosis. The Office Action cites Björklund as teaching that the antibody can be used in different immunoassays. Björklund does in fact hypothesize that the "rate of cell apoptosis may

be used in the diagnosis of diseases with involvement of apoptosis, such as degenerative diseases and cancer, and in the monitoring of the effect of therapy." However, there is no teaching or disclosure regarding what *type* of therapy could be monitored. In fact, there is no teaching or suggestion whatsoever related to how one would use the disclosed antibody to monitor the effect of therapy, much less how one would use the disclosed antibody in the presently claimed invention.

Schlossman teaches an antibody which binds to epitope localized on the membrane of mitochondria, 7A6, which is only present in cells undergoing apoptosis. Schlossman does in fact hypothesize that the disclosed antibody can be used for many uses, including a use "to monitor the efficacy of therapeutic regimens . . . ." However, there is no teaching or disclosure regarding what *type* of therapeutic regimen could be monitored by the use of the antibody. In fact, there is no teaching or suggestion whatsoever related to how one would use the disclosed antibody to monitor the effect of a therapeutic regimen, much less how one would use the disclosed antibody in the presently claimed invention.

Desjardins discloses the need for markers of apoptosis in order to determine whether apoptosis has been induced in tumor cells by cancer chemotherapy. Desjardins is cited as teaching that anti-GP46 can be used in methods that require the specific targeting of apoptotic cells. Desjardins does in fact hypothesize that the disclosed antibody can be used "for the detection of apoptosis . . . to monitor the treatment of disease," and specifically mentions that the disease could be cancer. However, there is no teaching or disclosure regarding what *type* of treatment could be monitored. In fact, there is no teaching or suggestion whatsoever related to how one would use the disclosed antibody to monitor the effect of treatment of disease, much less how one would use the disclosed antibody in the presently claimed invention.

Thus, Applicants respectfully submit that the Office Action has failed to establish a *primia facie* case of obviousness, because all of claim limitations are not taught or suggested by either the primary reference Meyn, or the combination of the Meyn reference with Riss, Björklund, Schlossman, and/or Desjardins. The Office Action argues that it would have been obvious to one of ordinary skill to use any of the antibodies taught by Riss, Björklund, Schlossman, or Desjardins in a method of monitoring the efficacy of chemotherapy in an individual; tellingly, even the Office Action does not assert that any such method is taught or suggested by any of these references. Further, the Office Action argues that one skilled in the art would have been motivated to use any of these antibodies in the unspecified method with a reasonable expectation of success by the teachings of Meyn on apoptosis as a feature of tumor response to chemotherapy in vivo, and the teachings of Björklund, Schlossman, and Desjardins for teaching that the M30, the anti-7A6, and the anti-GP46 antibodies are available for monitoring the effect of therapy or determining whether apoptosis has been induced in tumor cells by chemotherapy. Further, the Office Action argues, without explanation, that one skilled in the art would have been motivated to substitute conventional assays of tumor size measurement for unspecified assays based on antibody binding merely because Desjardins teaches that the conventional assays require at least a month of treatment. The mere description in Meyn, however, that apoptosis *may* be a potential response to treatment with a chemotherapeutic or chemopreventive agent does not amount to a teaching or suggestion that a response to administration of a chemotherapeutic or chemopreventive agent to an individual could be *determined* by measuring biological markers to apoptosis. There is no evidence in either the cited prior art or the argument in the Office Action in support of this ground of rejection that any unspecified method could utilize the existence of apoptosis as a result of

chemotherapeutic treatment to determine whether the patient had responded to the treatment. Given the fact that Riss, Björklund, Schlossman, and Desjardins are concerned merely with describing specific antibodies to biological markers associated with apoptosis, they do not contemplate that a response to administration of a chemotherapeutic or chemopreventive agent could be determined by collecting tissue or cell samples before and after exposure to the chemotherapeutic or chemopreventive agent and immunohistochemically measuring the optical density of the cells stained with the antibodies that have been detectably labeled. In the absence of such teaching, Applicants contend there was simply no motivation to combine these references. Once again, it is Applicant's position that the obviousness rejection based on this combination of references in the Office Action has been achieved through the use of impermissible hindsight, and that the pending claims are non-obvious over the cited prior art, taken alone or in any combination.

For the reasons set forth above, Meyn, Riss, Björklund, Schlossman, and Desjardins do not disclose, either individually or in combination, a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests withdrawal of this rejection and requests reconsideration of the claims.

Claims 1, 2, and 4-6 are rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Meyn in view of Riss, Bjorklund, Schlossman, and Desjardins, and further in view of Bacus I. Applicants respectfully traverse this rejection.

None of the cited references, alone or in combination, teach or suggest the instantly claimed method. The teachings and deficiencies, as related to the present invention, of Bacus I is

discussed above. In addition, the teachings and deficiencies, as related to the present invention, in view of Meyn, Riss, Bjorklund, Schlossman, and/or Desjardins are discussed above. The deficiencies of Meyn, Riss, Bjorklund, Schlossman, and Desjardins are not overcome by the combination with Bacus I.

Applicants respectfully submit that the Office Action has failed to establish a *primia facie* case of obviousness, because all of claim limitations are not taught or suggested by Meyn, in view of Riss, Bjorklund, Schlossman, and Desjardins, and further in view of Bacus 1. The Office Action argues, without citation to the art, that it would have been obvious to one of ordinary skill to include a DNA stain with the detectably labeled antibody and perform image analysis by splitting a signal comprising the optical density of the stained biological sample into a multiplicity of signals which are processed using optical filters having different absorption and transmittance properties, so that each signal is specific for one of a multiplicity of stains used to stain the cells in the biological sample. Further, the Office Action argues that one of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Bacus 1 on the inclusion of a DNA stain to determine the total number of cells in the sample. Further, the Office Action argues, without explanation, that one of ordinary skill in the art would know that the DNA stain would serve to quantify the total number of cells and thus the ratio of antibody stain to the DNA stain would give the percentage of apoptotic cells in a sample.

However, as stated above, Meyn, Riss, Björklund, Schlossman, and Desjardins do not disclose, either individually or in combination, a *method* for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. This deficiency is not remedied by consideration of the teachings of the Bacus I reference, which teaches merely

how to *prognosticate* or *predict* a response to a chemotherapy by obtaining a single biopsy from a human having a cancer. Even if taken as providing teachings of a method (which Applicants understand is *not* the position taken in the Office Action, which for reasons set forth with respect to the previously-discussed ground of rejection is believed to be satisfied by the references other than Bacus I cited in this ground of rejection) the Bacus I reference certainly does not teach or suggest the presently claimed methods that require collecting both a first and second tissue or cell sample from an individual, both before and after exposing the individual to a chemotherapeutic or chemopreventive agent. In the absence of such teaching, Applicants contend there was simply no motivation to combine these references. Once again, it is Applicant's position that the obviousness rejection based on this combination of references in the Office Action has been achieved through the use of impermissible hindsight, and that the pending claims are non-obvious over the cited prior art, taken alone or in any combination.

For the reasons set forth above, Meyn, Riss, Björklund, Schlossman, Desjardins, and Bacus I do not disclose, either individually or in combination, a method for determining a response to administration of a chemotherapeutic or chemoprevention agent to an individual. Accordingly, Applicant respectfully requests withdrawal of this rejection and requests reconsideration of the claims.

Claims 1, 2, 4 and 5 are rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Meyn in view of Riss, Björklund, Schlossman, and Desjardins, and further in view of Booth et al. (Apoptosis, 1996, vol. 1, pp. 191-200) ("Booth"), the abstract of Shen *et al.* (Cancer, 1998, vol. 82, pp. 2373-2381) ("Shen"), the abstract of Hiraishi *et al.* (Glycobiology, 1993, vol. 3, pp. 381-390) ("Hiraishi"), the abstract of Cutrona *et al.* (J. Experimental Medicine,

1995, vol. 181, pp. 699-711) ("Cutrona"), and the abstract of Frankfurt *et al.* (Anti-Cancer Res., 1996, vol. 16, pp. 1979-1988) ("Frankfurt"). Applicants respectfully traverse this rejection.

The teachings and deficiencies, as related to the present invention, of in view of Meyn, Riss, Björklund, Schlossman, and Desjardins are discussed above. The deficiencies of Meyn, Riss, Björklund, Schlossman, and Desjardins are not overcome by the combination with the additional cited art.

Booth is cited as teaching that antibodies raised to the peptide DVVDADEYLIPQ are useful markers of apoptotic cells in the intestinal epithelium. Shen is cited as teaching that the Ki-67 antibody is indicative of apoptosis. Hiraishi is cited as teaching that antibodies that bind to Le(y) are indicative of apoptosis. Cutrona is cited as teaching that expression of CD10 and CD38 on the surface of lymphoma cells was indicative of the cells undergoing apoptosis. Frankfurt is cited as teaching that monoclonal antibodies that bind to single-stranded DNA are indicative of apoptosis. Attallah, which is also mentioned in this rejection, is cited as teaching that antibodies that bind to CK1 can be used to quantify apoptotic epithelial cells in premalignant lesions of the gastric mucosa. However, none of the cited references teaches or suggests a method or assay, and neither Booth, Shen, Hiraishi, Cutrona, Franfurt, nor Attallah teach that the disclosed antibodies could be used for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual, much less teach that such an antibody could be used in a method of the claimed invention.

Thus, Applicants respectfully contend that the Office Action has failed to establish a *primia facie* case of obviousness, at least because all of claim limitations are not taught or suggested by Meyn, in view of Riss, Björklund, Schlossman, and Desjardins, and further in view of Booth, Shen, Hiraishi, Cutrona, and Frankfurt. The Office Action argues that it would have

been obvious to one of ordinary skill in the art to use any of the above antibodies in the method of detecting apoptosis as a result of chemotherapy. Further, the Office Action argues that one skilled in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Booth, Shen, Hiraishi, Cutrona, Frankfurt, and Attallah for teaching alternative antibodies which specifically bind to apoptotic markers. However, as stated above, Meyn, Riss, Björklund, Schlossman, and Desjardins do not disclose, either individually or in combination, any method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Further, because Booth, Shen, Hiraishi, Cutrona, Frankfurt, and Attallah merely describe specific antibodies to biological markers associated with senescence, apoptosis, and/or terminal differentiation, they also do not contemplate a method for determining or monitoring a response using these specific antibodies, much less a method of the present invention of determining a response by immunohistochemically staining two samples removed from an individual, both before and after exposure to the treatment, and measuring the optical density of the stained cells. In the absence of such teaching, Applicants contend there was simply no motivation to combine these references. Once again, it is Applicant's position that the obviousness rejection based on this combination of references in the Office Action has been achieved through the use of impermissible hindsight, and that the pending claims are non-obvious over the cited prior art, taken alone or in any combination.

For the reasons set forth above, Meyn, Riss, Björklund, Schlossman, Desjardins, Booth, Shen, Hiraishi, Cutrona, Frankfurt, and Attallah do not disclose, either individually or in combination, a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests withdrawal of this rejection and requests reconsideration of the claims.

Claims 1, 2, 4 and 5 are rejected under 35 U.S.C. § 103(a) as being unpatentable for obviousness over Meyn in view of Riss, Björklund, Schlossman, and Desjardins, and Bacus I, and further in view of Pamukcu *et al.* (U.S. 5,852,035) ("Pamukcu"), Smith-McCune *et al.* (WO 99/24620) ("Smith-McCune"), and the abstract of Attallah *et al.* (Hepato-Gastroenterology, 1996, Vol. 43, pp. 1305-1312) ("Attallah"). Applicants respectfully traverse this rejection.

None of the cited references, alone or in combination, teach or suggest the instantly claimed method. The teachings and deficiencies, as related to the present invention, of Meyn in view of Riss, Björklund, Schlossman, and Desjardins, and further in view of Bacus I, is discussed above. The deficiencies of Meyn, Riss, Björklund, Schlossman, Desjardins, and Bacus I are not overcome by the combination with the additional cited art.

Pamukcu is cited as teaching a method for treating pre-malignant lesions including colonic polyps and cervical dysplasia by administering compounds that induce apoptosis in the neoplastic tissues. Smith-McCune is cited as teaching methods of screening for cervical dysplasia and cervical cancer comprising the measurement of apoptotic cells in cervical samples. Smith-McCune is also cited as teaching that the apoptotic rate is unregulated in dysplastic tissue. Attallah is cited as teaching that antibodies that bind to CK1 can be used to quantify apoptotic epithelial cells in premalignant lesions of the gastric mucosa. However, Pamukcu, Smith-McCune, and Attallah do not teach or even suggest the presently claimed invention of collecting both a first and second tissue or cell sample from an individual, both before and after exposing the individual to a chemotherapeutic or chemopreventive agent, and measuring the optical density of cells after immunohistochemically staining them with a detectably labeled antibody directed against a biological marker associated with, *inter alia*, apoptosis.

Thus, Applicants respectfully contend that the Office Action has failed to establish a *primia facie* case of obviousness, because all of claim limitations are not taught or suggested by Meyn, in view of Riss, Bjorklund, Schlossman, and Desjardins, and Bacus I and further in view of Pamukeu, Smith-McCune, and Attallah. The Office Action argues that it would have been obvious to one of ordinary skill in the art to use the method asserted previously by the Office Action to be obvious by the combination of Meyn, Riss, Bjorklund, Schlossman, and Desjardins in a method of determining a response to a chemopreventive agent, such as taught by Pamuku, in an individual having pre-malignant lesions or dysplasia. Further, the Office Action argues that one of skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Pamuku on the induction of apoptosis in pre-malignant lesions as a target for therapy, the teachings of Smith-McClune on the correlation between apoptotic rate and dysplasia, and the teachings of Attallah on the use of antibodies to quantify apoptosis in pre-malignant lesions.

However, as stated above, Meyn, Riss, Björklund, Schlossman, Desjardins, and Bacus I do not disclose, either individually or in combination, a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Further, Pamukeu, Smith-McCune, and Attallah do not even contemplate a method for determining or monitoring a response using the specific antibodies disclosed in each of the additionally-cited references, much less a method of the present invention of determining a response by immunohistochemically staining two samples removed from an individual, both before and after exposure to the treatment, and measuring the optical density of the stained cells. In the absence of such teaching, Applicants contend there was simply no motivation to combine these references. Once again, it is Applicant's position that the obviousness rejection based on this

combination of references in the Office Action has been achieved through the use of impermissible hindsight, and that the pending claims are non-obvious over the cited prior art, taken alone or in any combination.

For the reasons set forth above, Meyn, Riss, Björklund, Schlossman, Desjardins, Bacus II, Pamukcu, Smith-McCune, and Attallah do not disclose, either individually or in combination, a method for determining a response to administration of a chemotherapeutic or chemopreventive agent to an individual. Accordingly, Applicant respectfully requests withdrawal of this rejection and requests reconsideration of the claims.

**Conclusion**

In view of the above amendments and remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue. If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned attorney as indicated below.

Respectfully Submitted,

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